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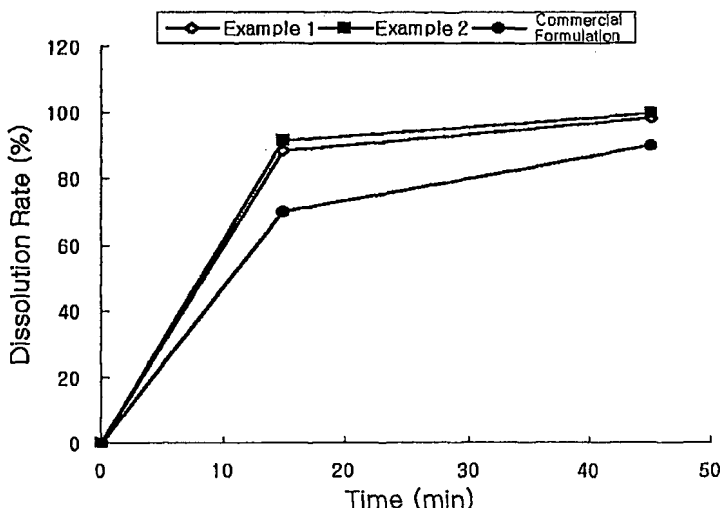
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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(54) Title: FORMULATION OF STABLE FOR MOISTURE ABSORPTION AND QUICKLY DISSOLVED TABLET CONTAINING CEFUROXIME AXETIL AND IT'S MANUFACTURING PROCESS



(57) Abstract: The present invention relates to a method and pharmaceutical composition for preparing an amorphous cefuroxime axetil-containing tablet which is rapidly disintegrated and absorbed in the gastrointestinal tract. In the inventive method, amorphous cefuroxime axetil is used as an active ingredient, and sodium starch glycolate is used to prevent the gelling of cefuroxime axetil and to promote the disintegration of cefuroxime axetil. The present invention allows the preparation of a rapidly disintegrating tablet formulation which is highly stable to moisture penetration upon short-term and long-term storage, does not cause the gelling of its components, and shows excellent dissolution rate even upon long-term storage.

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FORMULATION OF STABLE FOR MOISTURE ABSORPTION AND QUICKLY  
DISSOLVED TABLET CONTAINING CEFUROXIME AXETIL AND IT'S  
MANUFACTURING PROCESS

5    **Technical Field**

          The present invention relates to a method and composition for preparing an amorphous cefuroxime axetil-containing oral tablet which is stable to moisture  
10 penetration during storage and exhibits fast dissolution rate.

**Background Art**

15           As disclosed in GB Patent No. 1,453,049, cefuroxime is an antibiotics having high activity against a wide variety of gram-positive and gram-negative microorganisms. Cefuroxime and salts thereof have insufficient fat solubility to pass through a biological membrane and thus  
20 are not sufficiently absorbed from the gastrointestinal tract. For this reason, they have been used only as injections.

          To solve this problem of cefuroxime, cefuroxime axetil, a prodrug-type compound, was developed which has  
25 increased fat solubility making oral administration possible. Cefuroxime axetil is an ester derivative where the 4-carboxyl group of cefuroxime was substituted with a 1-acetoxyethyl group. As disclosed in GB Patent No. 1,571,683, the attachment of 1-acetoxyethyl ester to  
30 cefuroxime results in an increase in fat solubility, thus promoting the absorption of cefuroxime from the gastrointestinal tract. Cefuroxime axetil is hydrolyzed rapidly in intestinal mucosa and blood after oral

administration, to exhibit the effect of cefuroxime.

As disclosed in GB Patent No. 2,127,401, cefuroxime axetil is advantageously used in an amorphous form. Regarding dose and administration for adults, cefuroxime  
5 axetil is administered twice daily at 250 mg each time in pharyngitis or tonsillitis symptoms, and may be administered twice daily at an increased amount of 500 mg each time in severe infections or a infection caused by low-sensitivity bacteria. Also, in a simple urinary tract  
10 infection, it is administered twice daily at 125 mg each time.

Cefuroxime axetil is a poorly soluble substance and forms gel upon contact with aqueous medium at 37°C. It was found that this gel formation delayed the disintegration of  
15 a formulation containing cefuroxime axetil, resulting in a reduction in dissolution and bioavailability, thus leading to a reduction in the effect of cefuroxime axetil. This fact can also be seen in a report indicating that when a cefuroxime axetil tablet is stored in a brown glass bottle  
20 at 40 °C and a relative humidity of 75% in an opened state, its moisture content is then increased 2-3% even in a time lapse of one month, and the time taken for the tablet to be disintegrated is at least 60 minutes (Japanese Journal, Antibiotics & Chemotherapy, Vol. 7, 11, 1991).

25 Korean Patent No. 73572 discloses a rapidly disintegrating, film-coated tablet in which a tablet core containing cefuroxime axetil is coated with a film showing a degradation time shorter than 40 seconds for preventing the gelling of cefuroxime axetil and for blocking the  
30 bitter taste in water-soluble medium. This tablet is commercially available under the trademark Zinnat® tablet

(Glaxo Smith Kline Co.). However, this tablet coated with the thin water-soluble film is readily penetrated with moisture during storage, and its tablet core can be degraded or deteriorated upon moisture penetration. For  
5 this reason, this tablet product must be thoroughly managed during its packing, distribution and storage. Otherwise, moisture can pass through the coating film and allows the surface of the tablet core to be gelled, thus reducing bioavailability.

10 In a solution to this problem, Korean Patent No. 299356 discloses a tablet containing large amounts of not only a pH adjuster of fine environment for maintaining the pH around cefuroxime axetil at an acidic pH but also silicon dioxide or a hydrate thereof as an antigelling  
15 agent. This tablet is commercially available under the trademark Bearsef tablet (Daewoong Pharmaceutical Co., Ltd.). However, this tablet has excellent stability but its total weight (615 mg) is 155 mg higher than that of Zinnat® tablet (460 mg). This is because it contains large  
20 amounts of silicon dioxide and a disintegrant as excipients, and this has many disadvantages in view of commercial factors and drug compliance.

#### Disclosure of Invention

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The present invention relates to a method and composition for preparing an amorphous cefuroxime axetil-containing oral tablet. The present invention has been made to solve the above-mentioned problems occurring in the  
30 prior art, and an object of the present invention is to provide a pharmaceutical composition of an amorphous

cefuroxime axetil-containing oral tablet which is not only highly stable to moisture penetration which can occur upon short-term and long-term storage, but also rapidly disintegrated and absorbed *in vivo*.

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#### Brief Description of Drawings

FIG. 1 is a graphic diagram showing the comparison of dissolution rates between a commercial tablet and tablets prepared according to Examples 1 and 2, in which the dissolution rates were measured in Test Example 1 after performing an acceleration test for 6 months (-◇-: a tablet of Example 1; -■-: a tablet of Example 2; and -●-: a commercial tablet (Zinnat®)).

15 FIG. 2 is a graphic diagram showing a change in the contents of a commercial tablet and tablets prepared according to Examples 1 and 2, in which the contents were measured after in Test Example 2 performing an acceleration test for 6 months (-▣-: a tablet of Example 1; -■-: a tablet of Example 2; and -□-: a commercial tablet (Zinnat®)).

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#### Best Mode for Carrying Out the Invention

25 The present inventors have conducted extensive studies to develop a cefuroxime axetil-containing oral formation, which can be prepared by a simple process, is more stable and shows rapid dissolution, as compared to Korean Patent No. 73572 or Korean Patent No. 299356. As a result of these studies, the present inventors have developed a tablet which is completely disintegrated into

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fine particles within at least one minute after the dissolution of its coating film by contact with artificial gastric juice. The components of the inventive tablet composition will now be described in detail.

5 (1) Active ingredient

In the inventive composition, amorphous cefuroxime axetil is used as an active ingredient.

(2) Excipients

The present inventors have found that, in order to  
10 inhibit the gelling of a drug with gelling properties, such as cefuroxime axetil, the attraction between drug particles must be maximally reduced while the drug particles must be dispersed in dissolution to the finest possible degree using various excipients. For this reason, cefuroxime  
15 axetil-containing oral tablet formulations were prepared adding various excipients. As a result, it could be confirmed that sodium starch glycolate is the most suitable excipient to inhibit gelling and to prepare a rapidly disintegrating oral formulation of cefuroxime axetil. The  
20 sodium starch glycolate has a characteristic in that it is swollen several hundreds times by the absorption of water. Thus, it provides a remarkable reduction in the gelling of cefuroxime axetil.

Furthermore, since the sodium starch glycolate  
25 particles have a small average particle size of 50  $\mu\text{m}$  and a spherical shape, they are uniformly distributed between cefuroxime axetil particles, thus reducing the attraction between the cefuroxime axetil particles. Thus, in order to make a rapidly disintegrating, film-coated cefuroxime  
30 axetil tablet, the sodium starch glycolate is contained at the amount of 20-100% by weight, and preferably 30-50% by

weight, relative to the weight of cefuroxime axetil taken as 100% by weight. This is because a sodium starch glycolate content of less than 20% by weight does not effectively prevent the gelling of cefuroxime axetil, and a  
5 sodium starch glycolate content of more than 100% by weight is excessively swollen, resulting in a reduction in its function as an excipient.

(3) Coating film

The present inventors have found that a tablet core  
10 needs to be coated with a film in order to inhibit moisture penetration into a cefuroxime axetil-containing tablet and to prevent a reduction in the content of cefuroxime axetil. In this case, it is preferred that a film coating base has a compact molecular structure and is not readily dissolved  
15 in aqueous solution. This is because the coating of the formulation with a polymer which is readily dissolved in aqueous solution can make water penetration easy, resulting in a reduction in the content of cefuroxime axetil, although it reduces the gelling of the tablet core.  
20 However, a water-soluble film coating base, such as Opadry AMB (Colorcon Ltd.) developed recently was reported to have excellent water-blocking effect as well.

The present inventors have conducted studies on a correlation between the thickness of a coating film and the  
25 gelling of cefuroxime axetil. The results showed that the lower the weight of the coating film, the gelling phenomenon did not occur, but resulted in a reduction of the content of cefuroxime axetil by moisture absorption. On the other hand, the higher the weight of the coating  
30 film, the content of cefuroxime axetil was not reduced, but cefuroxime axetil absorbed moisture during an acceleration test and thus exhibited the gelling phenomenon in a

dissolution test. Accordingly, the present inventors have conducted studies to determine the optimal coating film thickness showing not only excellent water-blocking effect but also no gelling phenomenon. Tablet cores prepared in Example 2 were placed into a Hi-coater. And, they were dispersed and coated with a conventional coating film-forming composition by a conventional method, in which the coating film-forming composition was used at varying amounts of 3.3, 4.3, 5.4 and 7.0% by weight relative to the total weight of the tablet core taken as 100% by weight. During two months after preparing the film-coated tablets while changing the weight of the coating film, the tablets were subjected to a stability test under storage conditions of 40 °C and 75% relative humidity in an opened state. In the stability test, the gelling and a reduction in the content of cefuroxime axetil according to a change in the coating film thickness were examined and the results are summarized in Table 1 below. As can be seen in Table 1, the optimal weight of the film coating film, which does not cause the gelling phenomenon and a reduction in the content of cefuroxime axetil, is 3.0-6.5% by weight, preferably 4.0-6.0% by weight, relative to the total weight of the tablet core taken as 100% by weight.

Also, the tablet cores were coated with Opadry AMB OY-C-7000A and OY-B-28920 (Colorcon Ltd.) that are film-coating bases with excellent moisture-blocking function.

Table 1: Stability test (gelling and reduction in content according to change in weight of coating film)

Coating film weight	3.3% by weight		4.3% by weight		5.4% by weight		7.0% by weight	
	Lapsed	Content	Gelling	Content	Gelling	Content	Gelling	Content



time	(%)		(%)		(%)		(%)	
0 day	100.2	X	99.7	X	99.4	X	99.9	X
15 days	97.4	X	99.4	X	99.2	X	100.2	X
30 days	94.4	X	98.4	X	98.7	X	99.8	0
60 days	91.2	X	96.1	X	99.0	X	99.9	0
Reduction in content	9.0		3.6		0.4		0.0	

(X: completely degraded without gelling; and 0: not degraded due to gelling)

#### (4) Preparing method

After mixing an active ingredient with excipients,  
 5 tablet cores can be obtained from the mixture using a  
 conventional punch. Such tablet cores can be coated with a  
 coating film-forming composition by an aqueous solution or  
 solvent method known in the art. The tablets can be coated  
 using a conventional coater, such as Manesty Accela-Cota,  
 10 Driam Coater or Hi Coater. The coated tablets can be dried  
 by standing in the coater or dried in a dry oven or high-  
 temperature drier.

The present invention will hereinafter be described  
 in further detail by examples. It will however be obvious  
 15 to a person skilled in the art that the present invention  
 is not limited to or by the examples.

#### Example 1

	Components	mg/Tablet
Group 1	Cefuroxime axetil	Amount corresponding to 250 mg of cefuroxime
	Sodium starch glycolate	100.0
	Silicon dioxide	10.0
	Sodium lauryl sulfate	4.0
Group 2	Microcrystalline cellulose	45.0
	Magnesium stearate	2.5

Coating film-forming composition	
Hydroxypropylmethylcellulose2910	13.7
Titanium dioxide	5.8
Ethyl cellulose	3.4
Diethyl phthalate	2.1

The components of group 1 as described above were mixed together and granulated using a roller compactor.

5 The resulting granules were uniformly mixed with the components of group 2 and tableted using a conventional tableting machine. The coating film-forming composition was dissolved in ethanol and methylene chloride, and then coated on the tablet core by a conventional method at the

10 amount of 4.0-6.0% by weight relative to the total weight of the tablet core taken as 100% by weight.

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Example 2

	Components	mg/Tablet
Group 1	Cefuroxime axetil	Amount corresponding to 250 mg of cefuroxime
	Sodium starch glycolate	70.0
	Silicon dioxide	8.0
	Sodium lauryl sulfate	4.0

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Group 2	Microcrystalline cellulose	55.0
	Sodium starch glycolate	10.0
	Magnesium stearate	2.5

Coating film-forming composition	
Hydroxypropylmethylcellulose2910	13.7
Titanium dioxide	5.8
Ethyl cellulose	3.4
Diethyl phthalate	2.1

The components of group 1 as described above were mixed together and granulated using a roller compactor.

5 The resulting granules were uniformly mixed with the components of group 2 and tableted using a conventional tableting machine. The coating film-forming composition was dissolved in ethanol and methylene chloride, and then coated on the tablet core by a conventional method at the

10 amount of 4.0-6.0% by weight relative to the total weight of the tablet core taken as 100% by weight.

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Example 3

	Components	mg/Tablet
Group 1	Cefuroxime axetil	Amount corresponding to 500 mg of cefuroxime
	Sodium starch glycolate	140.0

Group 2	Silicon dioxide	6.0
	Sodium lauryl sulfate	6.0
	Microcrystalline cellulose	90.0
	Sodium starch glycolate	20.0
	Magnesium stearate	5.0

Coating film-forming composition	
Partially hydrolyzed polyvinyl alcohol	12.4
Titanium dioxide	6.8
Talc	3.1
Lecithin	2.6
Xanthan gum	0.1

The components of group 1 as described above were mixed together and granulated using a roller compactor. The resulting granules were uniformly mixed with the components of group 2 and tableted using a conventional tableting machine. The coating film-forming composition was dissolved in distilled water, and then coated on the tablet core by a conventional method at the amount of 4.0-6.0% by weight relative to the total weight of the tablet core taken as 100% by weight.

#### Test example 1

In order to evaluate the formulations prepared in Examples 1-3, an acceleration test was performed. In the acceleration test, the film-coated tablets prepared in Examples 1-3 and a commercial cefuroxime axetil tablet were stored in transparent cases under storage conditions of 40 °C and 75% relative humidity in a sealed state for 6 months, and then a change in the content of cefuroxime axetil and the dissolution rate of cefuroxime axetil after 6 months were measured. The results are given in Table 2 for comparison.

Table 2: Stability test (comparison of content and dissolution rate)

		Example 1		Example 2		Example 3		Zinnat® tablet	
Storage time (months)		0	6	0	6	0	6	0	6
Content (%)		100.3	99.2	100.1	98.6	100.2	98.4	101.3	96.1
Reduction in content		2.1		1.5		1.8		4.2	
Dissolution rate (%)	15 min	93.6	88.6	90.9	86.4	89.4	85.4	72.8	70.5
	45 min	99.9	97.5	100.3	98.4	100.1	97.4	101.4	90.9

### Industrial Applicability

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As evident from the results of Test Example 1, the inventive formulation overcomes the shortcoming of instability to water penetration occurring in the prior art, by utilizing sodium starch glycolate as an agent for preventing the gelling of amorphous cefuroxime axetil and for promoting the disintegration of amorphous cefuroxime axetil. Thus, the inventive formulation is highly stable to moisture absorption upon short-term and long-term storage. In addition, the inventive formulation is a rapidly disintegrating tablet which is disintegrated rapidly within one minute after the initial disintegration of its coating film. Thus, it can help cefuroxime axetil being absorbed into the body rapidly, and has excellent dissolution rate upon not only short-term storage but also long-term storage, thus showing a significantly reduced difference in bioavailability according to storage time, unlike the prior formulations showing a difference in bioavailability according to storage time.

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**What Is Claimed Is:**

1. A composition for preparing a rapidly disintegrating, film-coated, cefuroxime axetil-containing oral tablet, the composition comprising cefuroxime axetil as an active ingredient, and sodium starch glycolate as an antigelling agent.

2. The composition of Claim 1, wherein the amount of the sodium starch glycolate is 10-50% by weight relative to the weight of cefuroxime axetil taken as 100% by weight.

3. The composition of Claim 1, which further comprises a coating film-forming composition at the amount of 3.0-6.5% by weight relative to the total weight of the tablet core taken as 100% by weight.

4. A method for preparing a rapidly disintegrating, film-coated, cefuroxime axetil-containing oral tablet, the method comprising the steps of:

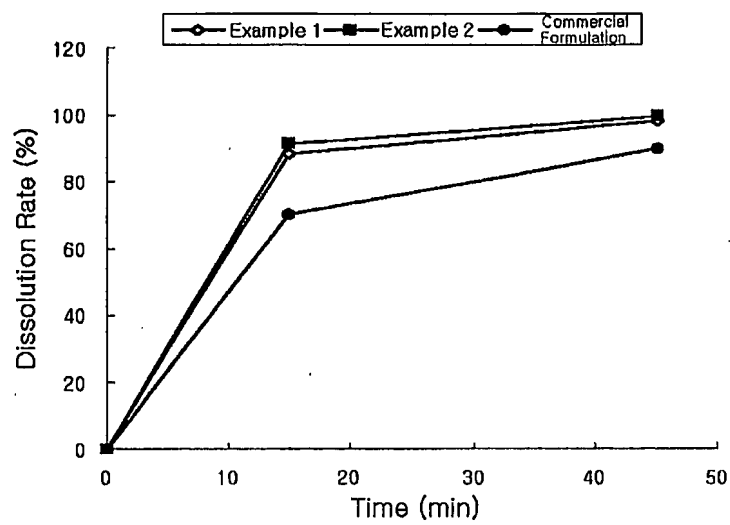
(A) granulating the pharmaceutical composition of Claim 1 using a roller compactor, to prepare a rapidly disintegrating granule;

(B) mixing the rapidly disintegrating granule with microcrystalline cellulose and tableting the mixture using a tableting machine; and

(C) coating the tablet core with a coating film-forming composition.

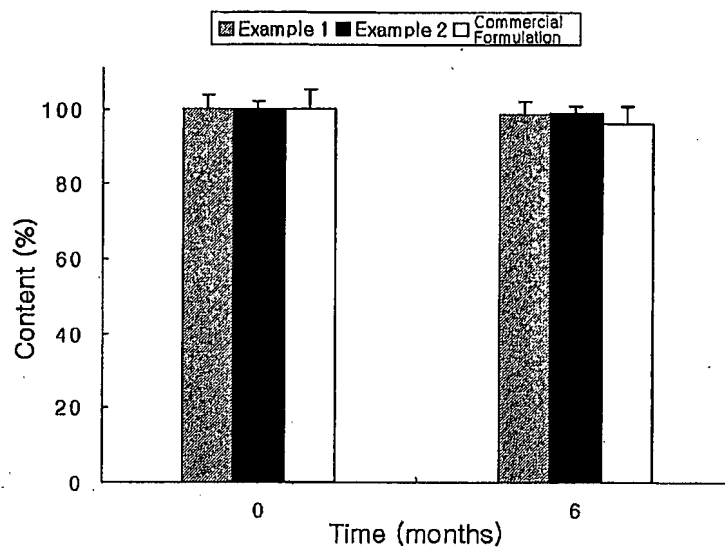
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FIG. 1



2/2

FIG. 2





# INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2004/001789

## A. CLASSIFICATION OF SUBJECT MATTER

**IPC7 A61K 9/22**

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
KOREAN PATENTS AND APPLICATIONS FOR INVENTIONS SINCE 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAPLUS(STN), WPI, USPTAFULL, JAPIO

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99-44616 A1 (DAEWOONG PHARMACEUTICAL CO., LTD) 10 September 1999. see entire document.	1-4
A	WO 99-62559 A1 (CAN) 09 December 1999. see entire document.	1-4
A	WO 2000- 76479 A1 (RANBAXY LABORATORIES) 21 December 2000. see entire document.	1-4

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

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"&" document member of the same patent family

Date of the actual completion of the international search

25 OCTOBER 2004 (25.10.2004)

Date of mailing of the international search report

**26 OCTOBER 2004 (26.10.2004)**

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# INTERNATIONAL SEARCH REPORT

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